PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Serge Louis Boulet et al.	Group Art Unit: 1626
Serial No.:	10/597,835	Examiner: Sun Jae Y Loewe
Application Date:	February 18, 2005	Conf No.: 6937
US Nat'l Entry Date (if applicable):	August 9, 2006	
For:	PHARMACEUTICAL COMPOUNDS	
Docket No.:	X-16288	

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

Applicants acknowledge acceptance of the RCE but note that the Examiner did not respond to the request not to enter the claim amendments (dated February 10, 2009) and has examined Claim 34. In order to facilitate prosecution, Applicants withdraw the request of non-entry of claim amendments submitted but unentered after final rejection. Applicants acknowledge Claim 34 is pending in the instant application. Applicants reserve the right to file a continuation application encompassing subject matter not currently claimed.

Claim Rejections under 35 USC 103(a)

The Examiner maintains the rejection of the elected species as currently claimed in Claim 34 as being obvious under 35 USC 103(a) in view of a certain compound disclosed in Cheshire *et al* as an inhibitor of nitric acid synthase (NOS). The Examiner states:

> "It is maintained that based on structural similarity, the prior art nitric oxide synthase inhibitor makes the instantly claimed compound obvious. One of ordinary skill would have a "reasonable" expectation of producing an additional NOS inhibitor by preparing a positional isomer. Applicant is invited to file a declaration showing unexpected results in order to overcome this ground of rejection."

Applicants maintain the assertion that the elected species as claimed in Claim 34 is not obvious in view of Cheshire *et al.* As the Examiner has failed to establish a *prima facie* case of obviousness, Applicants believe demonstration of unexpected results is unnecessary.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. MPEP §2143.

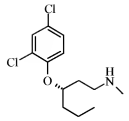
Applicants respectively submit that one skilled in the art of medicinal chemistry of nitric oxide synthase (NOS) inhibitors with the knowledge available in Beaton, H; *et al.*; *Biorganic & Medicinal Chemistry Letters*, 11 (2001) pages 1023 – 1026 would not have selected Compound A of Cheshire *et al.* as lead compound to arrive at compounds of the current invention as inhibitors of nitric oxide synthase. Applicants further submit even if a skilled artisan would be motivated to start with the Compound A., in view Beaton *et al.*, there would be no reasonable expectation that the structural modification employed would produce an inhibitor of nitric oxide synthase.

The United States Court of Appeals for the Federal Circuit has recently explained that within the chemical arts teaching, suggestion or motivation evolves from one of ordinary skill in the art selecting the prior art compound as lead compound to perform further modification, Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989 (Fed. Cir 2008):

> "An obviousness argument based on structural similarity between claimed and prior art compounds "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." Takeda, 492 F.3d at 1359; see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008) (stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art)."

No motivation to select the prior art compound, Compound A, of Cheshire *et al.* as a lead compound to make new inhibitors of nitric oxide synthase in view of Beaton *et al.*

Applicants assert, in view of Beaton *et al.*, one of ordinary skill in the art of medicinal chemistry would not select Compound A of Cheshire *et al.* (see Figure 1) as lead compound to make new inhibitors of nitric oxide synthase (NOS).



A.

Figure 1.

A skilled medicinal chemist seeking to make new inhibitors of NOS would select a lead compound which is a selective inhibitor of iNOS, the preferred isoform. Beaton *et al.* teaches compounds which are non-selective have undesirable cardiovascular side effects arising from inhibition of the isoform eNOS (see page 1023). Beaton *et al.* further distinguishes the importance of selective NOS inhibitors by disclosing the discovery of one of the most selective inhibitors known, compound **5j**. Compound **5j** is shown to be a potent inhibitor of iNOS with no significant activity toward the undesirable eNOS enzyme (see pages 1023-1024). A skilled artisan seeking to make alternate compounds as inhibitors of nitric oxide synthase would be motivated to select compound **5j** as a lead compound do to its properties as a selective inhibitor.

Cheshire *et al.* discloses certain of phenoxypropylamines including Compound A as inhibitors of nitric oxide synthase. However, Cheshire *et al.* makes no teaching as to which compounds may or may not be selective nor does it teach the desirability of selective compounds which lack eNOS activity. Thus, a skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would choose a lead molecule which lacks undesirable eNOS activity and not Compound A which is disclosed as a general inhibitor of nitric acid synthase.

No reasonable expectation that making a positional isomer of the compound disclosed in Cheshire *et al.* would lead to an inhibitor of nitric oxide synthase

Applicants assert in view of Beaton *et al.*, even if a skilled artisan would select Compound A as a lead compound, there would be no reasonable expectation that making a positional isomer modification would produce an inhibitor of nitric oxide synthase.

In exploring structural variation of the 3,4-dihydro-1-isoquinolinamines, Beaton *et al.* discusses the dramatic effects of positional isomer change on the inhibition of nitric oxide synthase. Moving a single substituent, in this case fluorine, one position demonstrated significant effects on activity. More specifically, moving a fluorine from the 5 to the 6 position, has little

effect, in that it maintains activity, while moving the same substituent one additional position, from the 6 to the 7 position, produces a compound which is essentially inactive (see Beaton *et al.* page 1024 Table 1). The following is a quotation from the Results and Discussion section on page 1024 (emphasis added):

> "Whilst fluorine substitution meta or para in the phenyl substituent or at positions 5 or 6 in the isoquinoline ring can be made with little or no effect on either the potency or selectivity profile of the compounds, dramatic effects occur on substitution at the isoquinoline 7 or 8 position. While the former is almost inactive, the latter results in a 34-fold increase in iNOS activity…"

These dramatic effects demonstrate the unpredictably of positional isomer changes in the medicinal chemistry of nitric oxide synthase inhibitors. Thus, a skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would not have a reasonable expectation that making a positional isomer of Compound A disclosed in Cheshire *et al.* would lead to an inhibitor of nitric oxide synthase.

In view of the above arguments and additional evidence, Applicants assert that the instantly claimed compound is not obvious in view of Cheshire *et al.* under 35 U.S.C. 103(a). Applicants respectively request allowance of Claim 34.

Applicants respectfully request consideration of the application and withdrawal of the rejection. Allowance of Claim 34 is kindly solicited. The Examiner is invited to contact the undersigned agent should any questions arise.

Respectfully submitted,

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June 24, 2009